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THE RELATION OF SYPHILIS TO MENTAL DISORDER AND THE TREATMENT OF G.P.I. BY MALARIA

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F.R.S.

DISCUSSION

The PRESIDENT said that the two papers formed an excellent opening to the discussion, and the Society was very much indebted to Dr. Nicol and Colonel James. The papers teemed with interesting points. He was particularly interested in the syphilis of children. He had now tried malarial treatment in about twenty-four children, and on the whole he had been rather disappointed with the effects of the treatment on the children themselves. The first case, however, was encouraging. It was a case of juvenile G.P.I., treated in 1926. The child to-day was alive and flourishing physically, but her mental condition was such that she could not be taught anything. He was wondering whether what he did for her was the wisest thing. But her blood and fluid to-day were normal serologically and in all respects, and had been so for five years. Therefore the malaria combined with arsenical treatment seemed to have killed the spirochætes, but the damage to her brain had been so severe that apparently she could not be taught. The history was only about four months, so that he thought it was a very favourable case upon which to test the treatment, and serologically it had responded.

He had treated other cases in which the nerve symptoms had been more marked, but the results had not been very encouraging. Personally, he felt that in the neuro-syphilis of children, when symptoms were present, it was hardly worth while to undertake treatment. If, on the other hand, the congenital neuro-syphilis were latent, that is to say, there were no clinical manifestations, and the positive cerebrospinal fluid were discovered on routine examination, then energetic treatment should be

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adopted, using tryparsamide and bismuth or tryparsamide and N.A.B., and later on giving malaria if the cerebro-spinal fluid remained positive.

Colonel James had mentioned that only some 600 cases or so had been treated by malaria over a certain number of years. Was Colonel James quite sure that more patients than 600 had not been treated? He himself had treated 24 cases altogether, and of this number Colonel James himself was responsible for 13—infected by mosquitoes, and the other 11 had been infected with blood from other cases. If other workers were like himself in that respect there might well have been very many more cases treated by malaria than figure in Colonel James's statistics, perhaps even as many again, *i.e.*, cases which had been infected with blood from other patients. If one had a patient with malarial blood available one did not want to trouble to send for the mosquitoes again, and it was a natural thing to do to infect with the blood. In Colonel James's opinion this method was not so good as that of the mosquito bite. He might be right, but frankly, the speaker could not himself see where the difference came in. He had children whose temperature went up to 106° or 107° when they had malarial blood injected into them, just the same as after the bite of the mosquito. He had one child infected with mosquitoes, and gave her a dose of bismuth afterwards, and the mosquito bites did not take. He did not know whether this was because of the bismuth or because the mosquito bite itself failed, for, as all knew, these bites did sometimes fail. But to that same child he gave blood from another patient, and that took very well. The subject was rather a difficult one to tackle. He had one child who was so delirious during the attacks that, not having the facilities for nursing such a case in his ward, the speaker had to cut his attacks short on that account.

As previously stated, on the whole, his experience with children had not been very encouraging. He had treated cases with malaria alone, and with malaria in conjunction with arsenical treatment, and they had shown a positive Wassermann afterwards, as they did before.

Dr. Nicol had mentioned the point about the diagnosis of early G.P.I. Such diagnosis was an extremely difficult thing to make. About twenty years ago he was at the Wakefield Mental Hospital when Dr. J. S. Bolton became

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Medical Superintendent, and Dr. Bolton suggested that they should carry out an investigation of the Wassermann test on early G.P.I. The diagnosis was made by Dr. Bolton, and he picked out certain cases which he thought might be early G.P.I. cases, and the speaker tested the blood and spinal fluid, but they were all negative. Dr. Bolton said that in the face of these negative Wassermanns the cases must be regarded as negative. This showed that it was very often difficult to diagnose an early G.P.I. case. If the blood and fluid were negative one should regard the case itself as negative.

Mr. DAVID LEES (Edinburgh) wished to congratulate Dr. Nicol and Colonel James on the most interesting accounts which they had given of their work at Horton Mental Hospital. His experience of this work during recent years extended to about 150 cases of neuro-syphilis which he had come in contact with in the routine work of the V.D. Clinic in the Royal Infirmary, Edinburgh. Some of these cases did not suffer from G.P.I. It was interesting to note that in the cases of neuro-syphilis seen in the Royal Infirmary during the past ten years, totalling 613 cases, the percentage of G.P.I. in female patients is much larger than that quoted by Dr. Nicol and others. There was no doubt that the cases were taken from a selected hospital population, and this might materially increase the incidence which was close on 17 per cent. of all cases of nerve syphilis in both sexes.

Dr. Nicol had stated that he had no difficulty in interrupting malarial fever with appropriate doses of quinine. His own experience in this respect had been disappointing. In any case of blood-inoculated malaria, in which he had tried to interrupt the fever temporarily, he had found that any dose, larger than $1\frac{1}{2}$ grains in twenty-four hours, was apt to terminate the fever completely, with the result that the strain was lost. He would like to ask the speakers if there were no other measures which they would suggest, which might control the hyperpyrexia which occurred in some cases without extirpating the infection. Two of his cases had ended fatally as a result of hyperpyrexia. In both of these cases quinine intravenously and intramuscularly, atebirin and other drugs had been administered and ice sponging had been applied. The strains with which these patients had been inoculated did not prove unduly severe or toxic

in other cases, and he was inclined to the view that the fatal result was due to some idiosyncrasy on the part of the patients. In both patients the type of malaria was benign tertian. The chief indication which he found for interrupting the fever was cardiac failure, and the worst type of case was not necessarily the patient with gross physical signs of cardiac disease such as aortic incompetence ; more serious were those cases in which the myocardium was damaged. It was certainly an advantage in all cases with any suspicion of cario-vascular disease, and a sound principle, to administer digitalis in some form from the time of inoculation right through the course of the illness until the termination of the fever.

The strains of malaria which he had used were three in number, benign tertian, ovale, and quartan. He had not had any experience of malignant tertian. Benign tertian malaria gave very excellent attacks of pyrexia, but the rapidly recurring rigors and attacks of pyrexia were apt to take too much out of the patient and put a great strain on the heart. His experience with ovale had not been satisfactory, as in three successive patients the infection died out after a small number of rigors. He was very satisfied during the last year with the results of quartan malaria. It gave a satisfactory pyrexial attack up to 104° to 105° . The interval between the attacks of fever was invaluable in allowing the patient to recover his strength, and it appeared to him that this strain should prove of the greatest value in advanced and debilitated cases with cardiac complications. The one disadvantage so far as he was concerned, was the long incubation period and the length of time during which the patient had to be hospitalised to complete the treatment of ten or twelve rigors. The principle which he adopted in treating every case of malaria was to have a clinical report and a careful examination of the blood and cerebrospinal fluid prior to administering malaria treatment. A similar examination was conducted after interrupting the fever, and one month later. It was interesting to note the changes which eventuated as a result of malaria therapy. The large percentage of cases which were treated showed chiefly an improvement in their mental outlook, their habits, their speech, etc. ; little or no change resulted in the blood or in the cerebrospinal fluid immediately after the attack of malaria or

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even one month later. It was largely on this account that he advocated the subsequent treatment of these cases with injections of tryparsamide and bismuth. The first course of treatment by this combination of drugs in most cases led to a further improvement in the clinical picture and alteration in the serological and cytological signs. He admitted that if this method were adopted in all cases it was not possible to assess the results of malaria treatment, but from comparison of patients treated by malaria alone and those treated by malaria followed by tryparsamide, he had no doubt in his mind that it was imperative to supplement malaria treatment with the administration of these other drugs. Dr. Nicol had stated that anti-syphilitic treatment did not necessarily prevent G.P.I.; his own personal opinion was that if every patient who suffered from syphilis was treated in the sero-negative stage, and was given an adequate amount of treatment, G.P.I. would become a very rare condition. He had some doubts as to the advisability of advocating malaria treatment in cases of systemic syphilis with the object of preventing the advent of neuro-syphilis. This work was being done chiefly in Vienna. There was no proof that any syphilitic patient would develop neuro-syphilis even if he had a resistant Wassermann test, and he questioned if we were justified in submitting any such patient to the risks of malaria therapy on the chance that it might prevent a later neuro-syphilis. He doubted also whether the average patient who had syphilis would submit to these risks. The better method of prevention in his view was to concentrate on earlier diagnosis, and on earlier and more intensive treatment. As things were at present, malaria therapy supplemented by continued treatment with tryparsamide and bismuth held out a prospect of recovery for approximately 30 per cent. of the cases of G.P.I. This type of treatment also was of considerable value in the intractable pains of tabes and in cases of neuro-syphilis, other than G.P.I., which proved resistant to treatment. He would like to ask Colonel James what, if any, difference there was between the pyrexia produced by malaria and by other agents, such as Sulfosin. Was it the pyrexia which wrought the change in the patient or was there some other factor. In his experience any other form of pyro-therapy either by T.A.B. vaccine, pyrifera, or by sulphur preparations had

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not given as good results as were obtained from malaria. There was no doubt that some of these methods of producing pyrexia were safer than inoculation by malaria, but none of them appeared to act in the same beneficial way on the patient's mental condition as did malaria. He would be interested to know if Colonel James would give them his views on how the fever did act, and with him he advocated further research on this subject, with a view to advancing our knowledge on the subject.

Mr. David Lees, in further remarks, asked Dr. Nicol what method he would adopt in the case of a juvenile G.P.I., aged 17, who had had seven inoculations of malaria and appeared to be immune, everyone of them failing to produce any pyrexia. The inoculations given had consisted of plasmodium ovale, benign tertian and quartan malaria of different strains. The only apparent reason for the immunity in this case was the statement that the mother of the child had suffered from severe malaria in India just prior to the birth of her child.

Another question which he wished to ask Colonel James was as to whether one was justified in giving anything such as injections of adrenalin to activate a malarial inoculation which was hanging fire. Some of his cases showed an abnormally long incubation period, and he would be glad to know if there was any preparation which might be administered with a view to stimulating a more rapid onset of the pyrexial attacks.

COLONEL L. W. HARRISON said that the two papers consolidated and crystallised the knowledge of this subject, and made clear some of the points on which there might have been a certain amount of confusion. He thought that Dr. Nicol gave the impression that the incidence of G.P.I. had not decreased during the last twenty years. Judging from the mortality returns of the Registrar-General, in 1919 there was a great decrease, from about 2,200 deaths to 1,600; the number now was between 1,100 and 1,200. That drop in 1919 was not due to malaria therapy, though no doubt for the continuation of the drop malaria had been responsible to a certain extent.

Another point referred to the efforts made to establish a special malarial centre. Colonel James and he had already inspected one place for this purpose, but, unfortunately, the matter was still hanging fire. He very

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much wanted to see that come to pass. It would be an enormous advance to have such a centre, for there were very many cases where people were unwilling to go to a mental hospital for this purpose, and there were also many cases in which there was strongly positive pathological cerebrospinal fluid more than about five years after injection, in which experience had shown that without malaria or tryparsamide an amelioration could not be produced. He was sure that large numbers of such cases would be benefited by malaria if it could be got easily, and it was only in such a centre as proposed that it could be done.

He wished it were possible to stimulate more people to voice a demand for malaria therapy under conditions in which it could be given with the greatest possible success. Colonel James and he had done their best, but perhaps if other people would voice their demand for such a centre the authorities would move a little more quickly in the matter.

Dr. BUCKLEY SHARP asked for any statistics as to the incidence of neuro-syphilis. He had in mind the question of the hospital suggested for the malarial treatment of potential neuro-syphilitics. It was well known that people could go through their lives with a positive blood Wassermann, and, many of them, quite happily without suffering any results from it. He was wondering whether that might also be the case with changes in the cerebrospinal fluid. If so, there would be obvious difficulty in persuading a patient, otherwise healthy, to undergo a treatment connected with which there was an appreciable risk—a mortality of some 10 per cent. It was not possible to assure the patients that if they did not have this treatment they would certainly become paralysed or insane, nor could they be assured that if they did have the treatment their cerebrospinal fluid would become normal, and they would be immune to neuro-syphilis in later life.

He had one case last year of a man who was infected in India with syphilis in 1913, and in 1914 he was supposed to have had malaria. The malaria attacks continued until about 1920. In 1931 he developed a rapidly progressive tabes. As a result of that experience the speaker got in touch with Colonel Berkeley-Hill, in charge of the mental hospital at Ranchi, India, and that

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gentleman sent him a booklet embodying the result of a questionnaire as to the incidence of neuro-syphilis both among Europeans and Indians in India who had had malaria. It was evidence that there was an appreciable incidence of neuro-syphilis in people, both Europeans and natives, who had had malaria in the ordinary way.

There was still one other difficulty in regard to the suggested hospital, namely, to get the patients to come in. A man would feel that by going to such a hospital the nature of his condition would be revealed to his friends, or at least there would be a vague suspicion as to what was wrong with him.

Dr. T. ANWYL DAVIES said that these cases were so difficult to treat, and that the crux of the position was, as several speakers had mentioned, the difficulty of diagnosis in the early stages of disease. He had had several early cases in whom symptoms had been little more than a headache, where diagnosis was confirmed by a positive Lange reaction of the paretic type. He believed that this reaction was one of the earliest signs, and that when obtained in cases who had no definite symptoms, these were potential cases of G.P.I. and must be vigorously treated as such.

Dr. H. M. HANSHELL warned against the too credulous acceptance of statements of patients from the Tropics that they had had repeated attacks of malaria. Few, if any, of these transient febrile attacks had been subjected to the only proof of malaria, namely, blood examinations; and even if most of them were malaria the paroxysms were too few to be considered as having any effect on a concomitant syphilis.

Dr. NICOL, in reply, said that he was interested in the remarks made by the President regarding congenital cases. He had not had a great deal of experience with congenital G.P.I.s. Since 1925 some eight cases had been admitted and in all cases treatment had been disappointing. At one time both mother and daughter were in the hospital together; the mother made a good recovery following malaria treatment but the girl died a year later, showing progressive deterioration.

Some speakers had mentioned that 5 grains of quinine were too much for aborting fever, as in some cases the attack of malaria failed to recrudescence. Dr. Nicol said that at Horton 5 grains were found to be the optimum

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dose, but that was with mosquito-inoculated cases. In blood-inoculated cases a smaller dose of quinine should be given, not more than 2 to 3 grains. The control of hyperpyrexia could generally be effected by tepid sponging, it is important to take the temperature frequently (every quarter of an hour) during the height of fever, in order to detect hyperpyrexia. Last year two cases developed a temperature of 108° , and it was necessary to abort these cases with quinine, for fear of a further high temperature forty-eight hours later. Both cases survived and the 5 grains of quinine were sufficient to produce a remission of fever.

It was difficult to assess the actual length of fever required for a satisfactory course. Dr. Nicol found that with the strain of benign tertian used at Horton it was necessary to terminate fever after about twelve to fifteen rigors. By interrupting a course of fever it was possible for a patient to have fever over a longer period, and this was always the case with quartan malaria. Most workers agreed that ten to twelve rigors were the optimum. On analysing the cases at Horton, it was found that there was a tendency to better results in those cases which had more than six to eight peaks of fever, but a very large series would be required to analyse this question more thoroughly. The same applied to the relative height of pyrexia. Malaria appears to give better results than other fever-producing agents, and it is possible that fever alone is not responsible, but something in the malaria toxin itself.

With regard to serological findings, changes did not become evident until a year or more following malaria therapy. At one time fluids were examined three months after treatment, but in nearly all cases the findings were the same as before treatment.

COLONEL S. P. JAMES also replied. He said that in order to cure G.P.I. with malaria it was necessary to have rather severe malaria for a certain length of time, and he doubted whether the malaria which was suffered by Europeans in the Tropics would be sufficient to act either as a cure or as a preventive. Europeans who had malaria in the Tropics were all treated by physicians very quickly, and in nearly all cases the malaria was cured on the second or third day. When they got a relapse they took quinine on the first day. They were always taking

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quinine, with the result that they did not get sufficient malaria to act as a cure or as a preventive of G.P.I.

In his paper he had stated that the number of patients treated by malaria in public mental hospitals in England and Wales in any one of the last five years had not exceeded 640. He did not know how many cases were treated outside; many were treated in the general hospitals of which no record was kept. The figures he had quoted were the official figures for county and county borough mental hospitals.

For aborting the malarial attack Mr. Lees used only 1 grain of quinine, and this probably sufficed in a case infected by blood inoculation, but 5 grains of quinine were necessary to abort the attack in the mosquito-infected cases. If 5 grains were given in most of the blood-inoculated cases, probably the malaria would be cured altogether.

The control of patients during the malarial attack should be by daily blood examination; if a striking increase in the number of parasites was found, treatment should be begun before there was a risk of hyperpyrexia. Unfortunately, atebrin was not much better in benign tertian than quinine, but it was remarkably more effective than quinine in malignant tertian. This knowledge could be usefully applied in connection with the patient referred to by Mr. Lees as being refractory to benign tertian infection. In that case, if benign tertian injections failed, malignant tertian should be tried. The malignant tertian should be watched very carefully and stopped by atebrin when there was any risk.

On the question of the manner in which malaria acts as a cure of general paralysis, the speaker believed that if Sir Walter Fletcher had lived he would have set up a proper investigation on the subject; he was still hoping that in time the Medical Research Council, whose duty it was to study this research problem, would get people to work upon it. Much more pressure was needed than was at present being exercised. In that connection he cordially agreed with what Colonel Harrison had said.